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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/029,479	10/21/1998	SARA LAVI	2290.00061(T	6118

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EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	24

DATE MAILED: 07/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/029,479	Applicant(s) LAVI, SARA
	Examiner Joseph Woitach	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-48,52-65 and 67-76* is/are pending in the application.

4a) Of the above claim(s) *45-48,52-64 and 67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65 and 68-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Prosecution Application

The request filed on May 1, 2002, paper number 22, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/029,479 is acceptable and a CPA has been established. An action on the CPA follows.

DETAILED ACTION

This application is a 371 national stage filing of PCT/IB96/01021, filed August 30, 1996 which claims benefit to provisional application 60/003,114, filed September 1, 1995.

Applicants' amendment filed May 1, 2002, paper number 23, has been received and entered. Claims 49-51 have been canceled. Claim 65 has been amended. Claims 68-76 have been added. Claims 45-48, 52-65 and 67-76 are pending. Claims 45-48, 53-64 and 67 are withdrawn from consideration as being directed to a non-elected invention. Claims 65 and 68-76 are currently under examination as they are drawn to the elected invention of group 5 drawn to treating cancer in a patient by administering a nucleic acid encoding PP2C alpha (see election filed October 23, 2000, paper number 11).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 65 stands and newly added claims 68-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Amendment to claim 65 to encompass detecting a type of cancer wherein the PP2Ca gene activity in the cells is decreased is noted. Claim 69 is a newly added claim drawn to introducing a vector into cancerous cells. While the claim is not drawn specifically to treating cancer, in light

of the teaching and guidance in the present specification, the only reason for the administration and expression of PP2Ca in the cancer cells of a subject is for the treatment of cancer. The instantly claimed method does not appear to be a new means for the delivery of a vector to a cancer cell, rather it relies on the methods known in the art for the delivery of the PP2Ca transgene. Upon review of the entire disclosure, no other purpose is proposed for the introduction of a vector expressing PP2Ca except for affecting gene therapy and for the treatment of cancer. Accordingly, newly added claim 69 and dependent claims 70-76 are being interpreted as methods of treating cancer by gene therapy.

As noted in the previous office action, the art teaches that various types of cancer do not show changes in PP2Ca expression when tested (Kitamura *et al.*). The present specification teaches that the expression of PP2Ca is decreased in some of the tumor samples tested, however the specification teaches that samples from other tissues show no or a varying change of expression and location of the PP2Ca in the cells tested (Example 4). Except in a statistically limited sample number, the present disclosure does not generally support a decrease in PP2Ca expression to be associated with cancer any and all cancers, nor does it support that PP2Ca is a direct cause or affect of the transformation process. As noted in the previous office actions, none of the working examples demonstrate that expression of PP2Ca can modulate the transformed phenotype of any human cancer or cancer cell line derived from a human. More importantly the data provided in the present disclosure derived from culturing transformed cell *in vitro* suggests that it is possibly the integration of the AAV, not PP2Ca expression which is important for the transformed phenotype. It is noted that certain isolated cell lines which were infected with AAV

demonstrate decreased PP2Ca expression (and a reduced transformed phenotype), however, the specification teaches that in cells that have lost their transformed phenotype because of the integration of AAV. Significantly, contrary to ameliorating a transformed phenotype, the specification teaches that the transfection and expression of PP2Ca restores the transformed phenotype/properties to these cells. The specification specifically teaches that PP2Ca 'has a key role in the initiation and/or maintenance of transformed cells' (page 33; lines 18-20). Contrary to any form of treatment, the only role for PP2Ca in cells supported by the instant disclosure appears to be to initiate and to maintain the transformed phenotype of cancer cells. It appears that the expression of PP2Ca in the cells of a subject will only initiate and/or maintaining a transformed phenotype in the cells of a subject. The specification fails to provide a nexus between the transforming capability of PP2Ca and affecting any form of treatment of any type of cancer. As acknowledged above, PP2Ca gene expression appears to be decreased in certain types of cancer in the limited number of samples tested, however as evidenced by the working examples in the present specification, it appears that the expression of PP2Ca will only enhance the transformed phenotype of the cancer cells in a subject.

As noted above claim 69 is being interpreted as a method of gene therapy for the treatment of cancer. However, even if the claim is literally interpreted and no therapy need be affected by the delivery of a vector capable of expressing PP2Ca in cancer cells, the specification fails to provide the guidance to why one would deliver a vector to a cancer cell or in what circumstances one would practice the instantly claimed method without affecting treatment. Clearly the method is directed to the delivery to and affecting of cancer cells, not delivery or

transforming normal cells. Additionally, it is noted that Applicants' have elected the invention drawn to treating cancer in a patient, not producing cancer in said subject. Though the claim appears to encompass possible affects outside the scope of the elected invention, for the sake of compact prosecution the claims are being interpreted as drawn to the elected invention.

The specification does discusses in general terms vectors which can be used in the claimed invention, and the examples provide more detailed guidance on the use of AAV as a possible vector. However, as previously noted, the experiments pointed to for support of an enabling disclosure are done *in vitro* with cell lines in culture. Though working examples are not required to provide an enabling disclosure, because of the unpredictability of gene therapy protocols recognized in the art (as reviewed by Verma and Anderson) detailed guidance to the specific types of cells to be targeted for gene expression and a means to target said cells, guidance to the required levels of expression of the inserted gene and a means to obtain and control said levels of expression are required. As argued above, the specification fails to clearly teach what a 'therapeutically effective amount' of any vector would be since any expression would appear to initiate and maintain a transformed phenotype. Further, the instant specification provides a general review of many possible vectors, however fails to provide a nexus between a proposed role of PP2Ca expression in transformed cells with the necessary guidance for the skilled artisan to alter said expression such that any treatment is achieved. There is no specific teaching to which types of cancers are associated with decreased expression of PP2Ca, and the specification is silent with respect to the necessary and detailed guidance on what receptors or ligand one should use to target a cancer cell. The instant specification relies on the teachings of

others for the delivery of a vector to cancer cells, however the specification fails to teach what specific cancer cells should be targeted, and if the art clearly teaches that these cells can in fact be targeted. As noted previously, the cited references and FDA approved protocol cited in Applicants previous arguments are not persuasive because they do not remedy the need for the specific guidance required to practice the instant invention. The protocols set forth in the cited references, represent different approaches for gene therapy but do not provide the necessary detailed guidance required to practice the specific methods as instantly claimed.

Applicants have proposed the expression of PP2Ca for the treatment of cancer in a patient, however essentially all of the work required to ultimately develop therapeutic methods has been left for others. Altered expression of a polynucleotide encoding PP2Ca may play a role in cancer, however the specification specifically teaches that the role of PP2Ca is for the initiation and/or maintenance of a transformed phenotype. At the time the claimed invention was made, the instant specification does not provide the necessary teaching to provide a nexus between the proposed methods in the instant application and the art recognized problems associated with gene therapy. As discussed above and the previous office action, there are several art recognized limitations and unpredictability issues regarding gene therapy, that include: vector to be used for gene expression, production of effective concentration of the candidate polypeptide, delivery of the gene to the appropriated target cell, sustained expression and production of the candidate protein *in vivo*, and maintaining an effective level of the enzyme *in vivo*. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). The present disclosure has not described nor provided examples of how the recited method of

gene therapy differs from those presently found in the art, and in great part rely on the methods of gene delivery established by others, Applicants face the same shortcomings faced by others skilled in the art with regards to the specificity of cell targeting and the ability to regulate gene expression.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 65 and 69-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically;

Claim 65 and 69 are vague and unclear in the recitation of 'detecting a type of cancerous cell in the patient wherein a decrease in PP2Ca gene activity is detected' because it is unclear how the cancer cells are detected and if all cancer cells will have reduced PP2Ca gene activity. It is unclear if the cancer cells are first detected then the level of PP2Ca determined, or if the level of expression of PP2Ca will determine the cell to be cancerous. Further, it is unclear what is meant or what is being distinguished by 'a type of cancerous cell'. It is unclear what types of cells to which the claim refers, only ones that have decreased PP2Ca, all cancer cells or a

particular subtype of cancer cell. In addition, the claims are unclear in the recitation of 'capable of targeting said cancerous cells' because the type of cancer being targeted is not specifically set forth. Further, it is unclear if the vector is targeted only to cancer cells or if it is capable of affecting other cancer or non-transformed cells. The metes and bounds of the claims are unclear because the vagueness of what cells are targeted and the nature of how the cells are specifically targeted or gene expression is affected. Dependent claims are included in the basis of the rejection because they fail to clarify the basis of the rejection. For example claim 71 recites general means of introducing a vector, and it is unclear how this will specifically target any cell. Claims 72-74 recite various potential types of targeting moiety, however it is unclear how the moieties are specifically associated with any type of vector. Claims 75 and 76 recite specific methodologies known in the art, however they fail to determine what type of cell is being detected, or how they are affected in a subject. Since the method is directed to treating a subject or affecting cancer cells in a subject, it is unclear how one would perform a Northern blot or Western plot in a subject, or if once cells are removed, how this will be used to determine the nature of the cells remaining in the subject, since cancer cells can be very heterogenous in nature.

Conclusion

No claim is allowed. As noted previously, the claims are free of the art of record because the art fails to teach a method of treating cancer in a mammal by gene therapy protocols in which the protein phosphatase 2C alpha is expressed, however the claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

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